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REMARKS

Applicants respectfully request reconsideration of this application in view of the above amendments and the following remarks.

This Amendment is mailed concurrently with a Petition for a **One Month** Extension of Time, along with an information disclosure statement and Form PTO -1449.

Claims 1, 3, 5, 6, 8, 10, 12, 14 and 15 are pending, of which claims 1, 6, 8, 10, 12, and 14 are independent. The remaining claims have been canceled.

Claim 8 was amended to further clarify that, as shown in, for example, Example 1 of the Specification, "small bowel motility" is improved using the composition of the present invention.

In the last Office Action, claims 1, 3, 5, 6, 8, 10, 12, 14 and 15 were rejected under Section 103(a) as obvious over Drug Launches (1993) in view of the acknowledged prior art, Schmidt et al. (US 5,424,064) ("Schmidt ('064)'), Holtmann et al. ("Holtmann") and Sable et al. ("Sable") for the reasons of record.

The Rejection of Claims 1, 3, 5, 6, 8, 10, 12, 14 and 15 under 35 U.S.C. §103(a) Over Drug Launches, in view of the acknowledged prior art, Schmidt (064), Holtmann, and Sable Has Been Overcome

Claims 1, 3, 5, 6, 8, 10, 12, 14 and 15 stand rejected under 35 U.S.C. §103(a) as obvious over Drug Launches, in view of the acknowledged prior art, Schmidt (064), Holtmann and Sable. Applicants respectfully disagree for the reasons that follow.

Applicants maintain that this combination of references does not teach or suggest the claimed invention. Drug Launches describes the product, "Purgo-Pil," in which bisacodyl is the sole active ingredient. As expressly shown in the Information Leaflet, a copy of which was previously submitted in Applicants' information disclosure statement and is also attached hereto, simethicone is neither present as an active substance nor as an excipient with the bisacodyl active ingredient in the tablet matrix. Rather, simethicone is present as an excipient in only the coating. Further, although the precise amount of simethicone used in the Purgo-Pil coating is not provided, it is clearly evident that only a trace amount could have been used because: 1) the simethicone was only used in the coating layer and not in the 10 mg bisacodyl tablet matrix; 2) the amount of simethicone used in the coating layer was in a diluted form; see Information Leaflet ("simethicone 30% emuls."); and 3) assuming that the coating is present on the tablet in an amount of from 5 % - 10% by weight of the uncoated Purgo-Pil tablet, the amount of simethicone used in the Purgo-Pil tablet could only be in an amount less than about 0.04 mg, which is well below Applicants' claimed range.

At best, Drug Launches, in combination with the Information Leaflet, teaches a laxative tablet containing a bisacodyl active ingredient, which is then coated with a coating that is "resist[ant] to gastric juice." Clearly, neither Drug Launches nor Information Leaflet discloses or suggests: 1) the combination

of simethicone with bisacodyl for purposes of improving the laxative effect of the bisacodyl; 2) the use of simethicone in amounts greater than trace amounts in the coating, which are too low to show any improved laxative effects; or 3) the use of "simethicone in an amount of about 10 mg to about 500 mg per dose" as claimed herein.

Holtmann reports on a study undertaken to compare simethicone with cisapride, a known treatment for gastro-oesophageal reflux disease, in treating functional dyspepsia. A full account of the study is given in the publication, "Randomized Double-blind Comparison of Simethicone with Cisapride in Functional Dyspepsia," *Aliment. Pharmacol. Ther.* (1999) 13:1459—1465 ("Holtmann Article"), which was also previously submitted in an information disclosure statement. The Holtmann study found that simethicone relieved the symptoms of dyspepsia during the first two weeks of treatment better than cisapride.

Dyspepsia, also known as indigestion, is a digestion disorder that is "usually applied to pain or discomfort in the lower chest or abdomen after eating." See The Bantam Medical Dictionary, p. 133 (copy attached). The Holtmann Article further provides that "agents that may affect gastrointestinal gas (e.g. simethicone...) are used for treatment of [patients having dyspepsia]." See Holtmann Article, page 1459. In fact, the Holtmann Article found that the "simethicone may stimulate gastrointestinal motility and therefore may accelerate the propulsion and expulsion of gas. See *Id.*, page 1464. Applicants respectfully submit that the Holtmann Article teaches the use of simethicone to treat upper gastrointestinal disorders, such as those involving the stomach like dyspepsia, by accelerating the propulsion and expulsion of gas. Applicants further respectfully submit that the Holtman Article fails to disclose or suggest: a) the use of simethicone to treat constipation or to improve small bowel motility as claimed herein; or b) the combination of simethicone with a laxative; or c) the combination of simethicone with specifically a bisacodyl laxative. In fact, Applicants' own data in Example 1 of the present application should also be noted. Applicants found the use of simethicone alone had no effect on small bowel transit in rats treated therewith.

According to the Office Action, Holtmann suggests that "increased gastric motility is an effect of simethicone." As defined on page 481 of Merriman Webster's Collegiate Dictionary, Tenth Edition (copy attached), "gastric" means "of or relating to the stomach." Assuming *arguendo* that this statement made in the Office Action is true, and given the context of the Holtmann indigestion study, such a disclosure would neither disclose nor suggest the affect that simethicone might have on lower bowel motility or laxation in general.

Schmidt ('064) is directed to the use of dimethylpolysiloxane in the treatment of reflux esophagitis. Schmidt neither discloses nor suggests: 1) the use of dimethylpolysiloxane for lower bowel motility or general laxative purposes; 2) the combination of dimethylpolysiloxane with other active agents; 3) the combination of dimethylpolysiloxane with a laxative, let alone a bisacodyl laxative; or 4) the use of bisacodyl in the treatment of reflux esophagitis.

Schmidt ('220), as acknowledged on page 1 of the Specification, discloses a dose of simethicone in approximately a 33% concentration, which is approximately equal to about 1670 mg, in the treatment of constipation. Not only is this amount of simethicone significantly higher than the upper limit of simethicone claimed in the present invention (500 mg), but Schmidt ('220) also fails to disclose or suggest the affect that simethicone may have on lower bowel motility as claimed. Moreover, Schmidt ('220) expressly teaches away from the combination of simethicone with a laxative, the latter of which Schmidt acknowledges as producing side effects such as, for example, increased potassium loss leading to increased constipation as well as increased calcium loss leading to osteoporosis. See Schmidt ('220), column 1, lines 24 – 56.

Enclosed is a complete copy of the Sable abstract, entitled "Treating GI Complications in the Diabetic Patient," Drug Therapy 63 – 77 (August 1989)("Sable Article"), which is also cited on the enclosed Form 1449 and included with the enclosed information disclosure statement. On page 74, Sable discloses the use of bisacodyl as a stimulant laxative in diabetic constipation. Sable neither discloses nor suggests the use of simethicone.

The differences between the cited prior art as discussed above and Applicants' invention as presently claimed is generally summarized in the below table:

<u>Reference Name</u>	<u>Reference Discloses</u>	<u>Reference Deficiencies</u>
Drug Launches, with Information Leaflet	Laxative tablet with bisacodyl laxative active	a) only uses <u>trace</u> simethicone (less than about <u>0.04 mg</u>); b) trace simethicone <u>only in coating</u> ; c) simethicone <u>not used as active ingredient</u>
Holtmann Article	Cisapride (GERD treatment) and simethicone for upper gastrointestinal disorders such as dyspepsia	Fails to teach: a) use of simethicone as laxative, as small bowel motility agent, or constipation agent; b) combination of simethicone with any laxative agents; and c) combination of simethicone with bisacodyl
Sable Article	bisacodyl as a stimulant laxative in diabetic constipation.	Fails to teach: a) simethicone; and b) lower bowel motility
Schmidt ('064)	dimethylpolysiloxane in the	Fails to teach:

	treatment of reflux esophagitis.	1) the use of dimethylpolysiloxane for lower bowel motility or general laxative purposes; and 2) the combination of dimethylpolysiloxane with other active agents, let alone laxative such as bisacodyl.
Schmidt ('220)	dose of simethicone in approximately a 33% concentration, in the treatment of constipation.	- simethicone dosage amount significantly above claimed simethicone range <u>-expressly teaches away</u> from combining simethicone with a laxative


Applicants respectfully submit that there is no disclosure or suggestion in the cited prior art to combine simethicone with a laxative, let alone with a bisacodyl laxative, to improve small bowel motility or treat constipation. In fact, the cited references either only taught the limited use of a simethicone active agent in gastric (stomach) related disorders, or expressly taught away from combining simethicone with laxatives. For these reasons, Applicants again submit that the claims as amended are patentable. Early and favorable reconsideration is requested.

Respectfully submitted,

McNally, et al.

By: 

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Dated:  July 2004

Att:

Information Leaflet -

PURGO-PIL 10 mg

NAME

PURGO-PIL 10 mg (Bisacodyl).

COMPOSITION

Active substance : Bisacodyl 10 mg.

Excipients : lactose - cellulose microcrist. - magnesium stearate per tablet.

Coating : talc - colophony - methacrylic acid and ethyl acrylate copolymer (1:1) - methacrylic acid and methyl methacrylate copolymer (1:1) - macrogol 6000 - povidone - titanium dioxide - simethicone 30% emuls.

PHARMACEUTICAL FORM

Box of 30 coated tablets resisting to gastric juice. Freely available in pharmacies.

GROUP

Laxative.

MANUFACTURER AND REGISTRATION OWNER

Laboratoria QUALIPHAR N.V./S.A. - Rijksweg 9 - B-2880 BORNEM

TO BE USED FOR

Treatment of the symptoms of constipation; facilitation of bowel motion in case of haemorrhoids. Evacuation before certain operations or examinations of the gastro-intestinal system.

CIRCUMSTANCES IN WHICH THE USE OF THE MEDICINE MUST BE AVOIDED

Children under the age of 4. Stomachache of which the cause is unknown, inflammation of the large bowel, acute abdominal affections, mechanical blocking of the intestine.

SPECIAL PRECAUTIONS

Prolonged use must be advised against. It is recommended to reduce the indicated dose with elderly persons, heart patients or persons with a poor functioning of the kidneys.

INTERACTION WITH OTHER MEDICINES AND FOOD

Abuse may influence the effect of diuretics and of digitalis products. An interval of 2 hours must be maintained between the taking of PURGO-PIL 10 mg and of dairy products or substances which neutralise or reduce acidity, such as bicarbonate and so on.

USE DURING PREGNANCY AND BREAST-FEEDING

The taking of PURGO-PIL 10 mg must be avoided during the first 3 months of the pregnancy. Although bisacodyl does not show up in the mother's milk, it may only be used on doctor's orders during breast-feeding.

INSTRUCTIONS FOR USE AND DOSES

In case of constipation: Children from the age of 10 and adults:

1 tablet per day, preferably in the evening, to be swallowed without chewing; not to be taken with milk or with a product against heartburn. Maximum 3 tablets per day. The effect of this tablet becomes noticeable after about 8 hours. When the tablets are taken before going to sleep, evacuation occurs in the morning. In intractable cases the dose can be increased to 2 tablets in the evening. Once the desired result has been achieved, one should try to extend the period between ingestion gradually (once every 2 days, then once every 3 days, and so on...), in order to avoid tolerance. It is recommended to combine the use of laxatives with food that is rich in fibres and with bodily exercise, and to keep exercising and taking such food after stopping the ingestion of the medicine. Chronic use of PURGO-PIL 10 mg must be avoided.

In preparation for an operation or examination: according to doctor's orders.

MODE AND ROUTE OF ADMINISTRATION

Coated tablets to be taken by mouth.

MEASURES IN CASE OF OVERDOSE

Symptoms of acute poisoning: stomach cramps, diarrhoea, dehydration. Notify a doctor as quickly as possible, phone the Antidote centre (070/245.245) or go to the emergency department of a hospital. Treatment: administration of water and mineral salts, under medical supervision.

UNWANTED EFFECTS

Sometimes: stomach cramps, diarrhoea. Abuse may cause irritation (tingling) and potassium deficiency and, in the long run, "lazy" bowels.

STORAGE

Store out of the reach of children. At room temperature (up to 25 °C) and in its original packaging. To be no longer used after the date stated on the packaging following the abbreviation "EX". The first two figures indicate the month, the next two or four figures the year. The expiry date is the first day of the stated month.

LATEST EDITION OF THE INFORMATION LEAFLET : 03.01.95

DIGESTIVE DRUGS

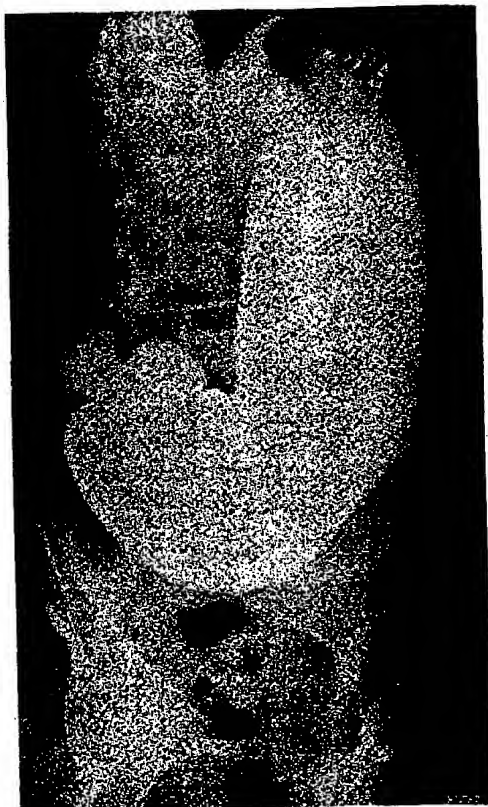
Treating GI Complications in the Diabetic Patient

Karen S. Sable, MD
Eugene M. Chang, MD

Much of the gastrointestinal dysfunction associated with long-standing diabetes has been attributed to autonomic neuropathy. The latest drug approaches, therefore, are targeted at correcting neuromuscular abnormalities. In diabetic gastroparesis, impaired neuromuscular activity is being effectively treated with prokinetic agents such as metoclopramide. Therapeutic options for diabetic diarrhea range from conventional antidiarrheal drugs to drugs such as clonidine and octreotide acetate (Sandostatin) that alter small bowel secretion and absorption. In patients with diabetic constipation, prokinetic agents appear to be the most promising approach.

Drugs Discussed in This Article:

Aldose reductase
inhibitors
(investigational)
Bethanechol chloride
Cholestyramine (Questran)
Cisapride
(investigational)
Clonidine
Dazopride (investigational)
Domperidone
(investigational)
Metoclopramide
Naloxone
Octreotide acetate
(Sandostatin)
Opiates
Phenolphthalein
Phenothiazines
Psyllium hydrophilic
mucilloid
Stimulant laxatives
Tetracycline



Gastrointestinal (GI) dysfunction has been reported in 20% to 76% of patients with long-standing insulin-dependent diabetes mellitus; it occurs most frequently in those with diabetic neuropathy, nephropathy, and retinopathy.¹⁻⁵ Table 1 shows the incidence of GI symptoms in 136 outpatients with diabetes.¹ Many of these intestinal complications can be attributed to autonomic neuropathy and are dependent on the severity of the neuropathy and the site and type of nerves involved. Regional neuromuscular, hormonal, and vascular pathology, and secondary processes such as infection, also contribute to the development of these complications.

Since the pathogenesis is not always clear and may be multifactorial, most conventional therapy is aimed at improving symptoms. Newer agents have been developed that improve motility or alter fluid and electrolyte transport in the GI tract of diabetics. This review examines both conventional and investigational therapies for three common GI complications of diabetes—gastroparesis, diabetic diarrhea, and diabetic constipation (Table 2).

DIABETIC GI COMPLICATIONS

GASTROPARESIS DIABETICORUM

Gastroparesis diabeticorum is a clinical syndrome characterized by delayed gastric emptying secondary to impaired gastric neuromuscular activity.¹⁻⁸ Gastroparesis diabeticorum occurs in about 27% of diabetics with neuropathy, whereas less severe abnormalities in gastric emptying can be found in about 57% of patients.³ It is manifested by anorexia, nausea, vomiting, early satiety, bloating, and abdominal pain; these symptoms can be intermittent or unremitting.

An upper GI x-ray (Figure 1) or endoscopy may be required to rule out other causes of the patient's symptoms. These studies may also confirm a diagnosis of gastroparesis. Caution should be used when administering anesthetics to patients with diabetic autonomic neuropathy, since they may be more prone to apnea and respiratory arrest. Both radiolabelled liquid and solid meals are more sensitive diagnostic indicators than barium of gastric retention.⁶ When these sensitive techniques are used, 22% of diabetics with no GI symptoms have radiologic evidence of gastric retention.¹

Supportive Therapy

Initial management of diabetic gastroparesis should be supportive. Correcting hyperglycemia with insulin may improve gastric motility.⁹

Discontinuing or adjusting the dosage of drugs that diminish gastric motility, eg, anti-

cholinergics, narcotics, tranquilizers, antidepressants, and ganglionic-blocking agents, may also help. In addition, fluid and electrolyte balance should be maintained. Nasogastric tube decompression can be used to remove retained stomach contents and allow the stomach to return to its normal size. This may reestablish normal gastric muscle tone that has been disturbed by distention. If these measures are not insufficient, the next therapeutic step should include "prokinetic" agents.

Table 1

GI Symptoms in 136 Diabetic Outpatients ¹	
Symptom	Incidence, %
Constipation	60
Abdominal pain	34
Nausea/vomiting	29
Dysphagia	27
Diarrhea	22
Fecal incontinence	20
None	24

Prokinetic Agents

A variety of prokinetic agents are being studied for use in diabetics to improve gastric emptying.

Metoclopramide decreases gastric emptying time by enhancing proximal gastric, fundic, and proximal small bowel smooth-muscle contractility. Because some actions of metoclopramide can be blocked by atropine and similar prokinetic effects are seen in postvagotomy patients, it has been suggested¹⁰ that the drug has a direct action—possibly cholinergic or antidopaminergic¹⁰⁻¹⁴—on gastric musculature. And while it does not in-

crease gastric acid secretion or stimulate gastrin release, it does increase lower esophageal sphincter tone. Metoclopramide also is a potent antiemetic, inhibiting dopa-

Metoclopramide decreases gastric emptying time by enhancing GI smooth-muscle contractility.

mine receptors in the chemoreceptor trigger zone of the brain.¹³ Several studies have suggested that prolonged administration of metoclopramide may result in tolerance and loss of metoclopramide's action on gastric emptying of liquids and that the drug's central antiemetic action may be

Figure 1

Gastric retention (shown by upper GI barium x-ray) with small bowel follow-through in a diabetic patient with neuropathy and gastroparesis.



At one hour, barium has still not left the stomach (a). A nasogastric tube has been placed 16 hours later. There is still retained barium in the patient's stomach; however, because there is no organic obstruction, barium has passed into the small and large intestines (b).

DIABETIC GI COMPLICATIONS

responsible for its relief of GI symptoms.^{13,15}

The recommended dosage of metoclopramide for diabetic gastroparesis is 5 to 15 mg, as a syrup or tablet, 30 minutes before each meal and at bedtime. The liquid may be the preferred form because the absorption of solid tablets in patients with delayed gastric emptying tends to be erratic and inadequate.

An injectable form, which is given intravenously (IV), subcutaneously (SC), or intramuscularly (IM), of a dosage of 10 mg four times daily, is available for patients unable to take the oral preparation. Subcutaneous metoclopramide can be easily injected by diabetics who administer their own insulin. The IV and IM forms, however, should only be used as a temporary measure (ie, for a few

days) prior to instituting another form. Rectal suppositories (25 mg) have been shown to be effective and especially useful for outpatient management.¹⁶

Approximately 10% of patients on metoclopramide experience adverse reactions.^{7,12,17} The most common side effects include diarrhea, drowsiness, fatigue, restlessness,

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Table 2

Therapeutic Agents for Diabetic GI Complications

Complication	Agent	Dosage	Reported Side Effects
Gastroparesis/diabeticorum	Metoclopramide	10 mg qid po 30 min before meals and qHS	Malaise, drowsiness, restlessness, insomnia, diarrhea, dystonic reaction, persistent dyskinesia, hyperprolactinemia
	Dominiprone	20 mg tid po 30-60 min before meals	Dry mouth, headache, diarrhea, restlessness, hyperprolactinemia, amenorrhea
	Cisapride	20 mg QID PO	Under investigation
	Ethiprione ¹	5 mg SC	Malaise, headache, nausea, abdominal discomfort, diarrhea, bronchial constriction
Diabetic Diarrhea	Clonidine ²	0.1 mg q12h slowly increased, as needed to 1.0-1.5 mg/d (apex dosage slowly when discontinuing the drug)	Dry mouth, sedation, hypotension
	Lidamine	2 mg tid po increased to 20 mg/d as needed	Under investigation
	Difluoride acetate (Sedostat) ³	50-150 mg q6-12h SC as needed	Exacerbation of diabetes, malabsorption, abdominal discomfort, drowsiness, hypertension
Diabetic constipation	Stimulant laxatives (bisacodyl, dantrolene, cascara sagrada, phenolphthalein)		Abdominal discomfort, electrolyte imbalance, cardiac disturbance, skin reaction, rare hepatotoxicity
	Metoclopramide ⁴		
	Cisapride ⁵		

¹Investigational drug

²Investigational use of approved drug

³Effectiveness suggested by anecdotal reports

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ness, and insomnia. These reactions are usually related to the dosage and duration of administration, so most can be improved by decreasing the dose of metoclopramide.

Extrapyramidal reactions, including dystonia, orolingual dyskinesia, bradykinesia, tremors, and torticollis, occur in about 0.2% of patients¹⁸; these symptoms can be treated with diphenhydramine hydrochloride, 50 mg IM, or benztropine mesylate (Cogentin), 1 to 2 mg IM. Irreversible tardive dyskinesia may also occur in rare cases and seems to be directly related to dosage and duration of therapy.

Metoclopramide may elevate serum prolactin levels and occasionally cause galactorrhea and gynecomastia.^{7,12} Rare cases of rash and neutropenia have been described in patients on metoclopramide, but no definitive causal relationship has been documented.

Preliminary studies are under way on dazopride, an agent that is structurally similar to metoclopramide. Although this agent does not cross the blood-brain barrier, it may stimulate gastric motility via peripheral cholinergic receptors.¹²

Domperidone is an investigational prokinetic agent with potent peripheral antidopaminergic activity comparable to that of metoclopramide.^{12,17,19} Recent reports indicate that domperidone provides both effective symptomatic relief of nausea and vomiting and primary treatment of esophageal

reflux and diabetic gastroparesis.^{17,19} However, domperidone lacks cholinergic activity and poorly penetrates the blood-brain barrier.

Domperidone has been shown to increase prolactin secretion and may result in breast enlargement, nipple tenderness, galactorrhea, and, less often, amenorrhea.¹² Other side effects include dry mouth, headache, diarrhea, and nervousness.

Domperidone appears to provide effective symptomatic relief of nausea and vomiting, and primary treatment of reflux and gastroparesis.

Horowitz recommends a dosage of 20 mg of oral domperidone 30 to 60 minutes before meals. His group also has shown that a single 40-mg dose improved diabetic gastroparesis.¹⁷ In addition, Heer has shown that domperidone, 10 mg IV, improves delayed gastric emptying.¹⁹ The drug is also formulated as a rectal suppository.

Cisapride is another investigational agent that stimulates the motility of the esophagus, stomach, and intestine.^{11,15} It is thought to facilitate acetylcholine release from neurons in the myenteric plexus, which subsequently stimulates muscarinic receptors on gut smooth-muscle cells. Cisapride does not affect gastric acid secretion. Unlike metoclopramide and domperidone, cisapride is not a dopamine antagonist and apparently provides only peripheral action.

In one study¹⁵ cisapride, 10 mg orally four times a day, continued to enhance gastric emptying of both liquids and solids after one month of therapy.¹⁵ This study also reported an increased frequency of bowel movements in patients on cisapride, but no other significant side effects were noted.¹⁹ These results are preliminary, and further studies need to be done to determine whether cisapride has fewer side effects than do other prokinetic agents.

Bethanechol chloride is another prokinetic agent being tested in gastroparesis.¹⁰ (In the United States, it is currently approved as a treatment for non-obstructive [functional] urinary retention.) This cholinergic agent stimulates gastric motility, increases gastric tone, and often restores rhythmic peristalsis.

Bethanechol, 5 mg SC, has been shown to improve gastric emptying¹⁰; it is also available in oral form. Side effects include diarrhea, malaise, headache, nausea, abdominal discomfort, and bronchial constriction. (Atropine is a specific antidote for overdose.)

Other Therapeutic Options

Combination therapy with prokinetic agents may be effective in diabetic gastroparesis and decreases the incidence of significant side effects. However, no controlled studies have been reported.

Aldose reductase inhibitors are under investigation and may reduce sorbitol production, which, in turn, may prevent or improve diabetic neu-

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ropathy. Other therapeutic measures for diabetic gastroparesis include antiemetics such as phenothiazine derivatives; while they have not been shown to affect gastric emptying, they may relieve nausea. Finally, more invasive therapy such as postbulbar feeding tubes and surgical procedures such as gastroenterostomy and pyloroplasty have been used. It should be noted that no significant benefit has been reported with surgical procedures; they should therefore be reserved as last resorts.

Gastric Bezoars

Bezoars are not uncommon in patients with diabetic gastroparesis (see Figures 2 and 3).²⁰ They form as a result of poor gastric emptying and are composed of retained nondigested vegetable matter. Bezoars can further obstruct the gastric outlet and lead to nausea, vomiting, and early satiety. A liquid diet, cellulase, and metoclopramide should provide symptomatic relief. Metoclopramide has been shown to inhibit reformation of bezoars by enhancing gastric emptying. Low-residue diets may also diminish recurrences. Endoscopic fragmentation should be reserved for refractory cases.

DIABETIC DIARRHEA

Diarrhea occurs in approximately 10% to 20% of patients with long-standing diabetes.^{1,3-5,21-24} Characteristically, the diarrhea is intermit-

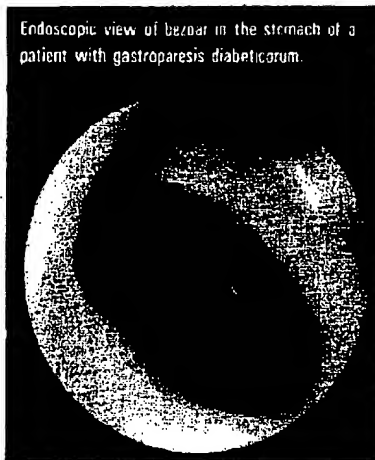
tent, but it can be persistent and very severe. Fecal incontinence, especially at night, may be a feature of diabetic diarrhea. It is probably due to sensory neuropathy and may require more specific work-up and treatment. Fecal incontinence due to other causes may also be wrongly reported as diarrhea.

Diarrhea occurs in approximately 10% to 20% of patients with long-standing diabetes.

Although the etiology of diabetic diarrhea is not well understood, it is almost always associated with autonomic neuropathy. Therefore, the absence of autonomic neuropathy should raise doubts about

Figure 2

Endoscopic view of bezoar in the stomach of a patient with gastroparesis diabeticorum.



the diagnosis of diabetic diarrhea.

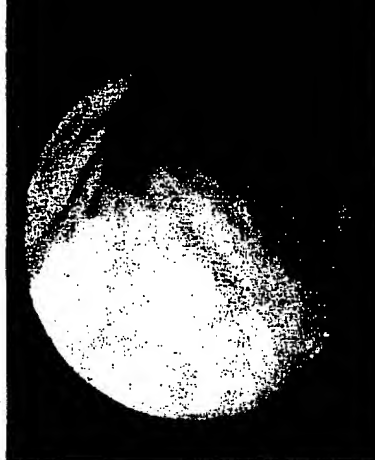
The diagnosis of diabetic diarrhea is usually made by excluding other causes of diarrhea. A careful history may uncover drugs, such as antacids, cathartics, prokinetic

drugs, and antibiotics, or excessive consumption of sorbitol that may exacerbate or cause diarrhea.

The patient should be asked to characterize stool frequency, consistency, and volume. Diarrhea in diabetics is usually watery, voluminous, and sporadic, with evidence of abnormal fluid and electrolyte transport in the diabetic small intestine.^{8,21,25-27} Medical conditions such as lactose intolerance, pancreatic insufficiency, infection, malabsorption, other endocrinopathies, and celiac disease are alternative causes that need to be ex-

Figure 3

Endoscopic view of bezoar in the stomach of a patient with gastroparesis diabeticorum. Gastric retention is secondary to abnormal gastric motility, and thus the widely patent pylorus can be seen at endoscopy.



cluded before the diarrhea can be attributed solely to diabetes. This may require upper and lower GI x-rays, endoscopy, small bowel biopsy, 24-hour stool collection, and tests for malabsorption.

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Various mechanisms have been proposed for the pathogenesis of diabetic diarrhea.^{1,4,5,21,23} In diabetics, small bowel motor abnormalities may lead to either increased or decreased transit time. However, small bowel transit times in diabetic neuropathy are not good indicators of the presence of diarrhea. Rapid transit may, itself, lead to diarrhea, and slow transit may lead to stasis, bacterial overgrowth, and blind-loop syndrome with resultant diarrhea. The role of colonic dysmotility in diabetic diarrhea is not known.

The absence of autonomic neuropathy raise doubts about the diagnosis of diabetic diarrhea.

Antidiarrheal Agents

If tighter blood glucose control does not decrease diarrhea, medications are available that may control mild cases. These include metoclopramide, opiates (codeine sulfate, tincture of opium), diphenoxylate hydrochloride with atropine, and loperamide (Imodium). Careful monitoring of patients on these agents is important since misuse may result in constipation.

The use of bulk-forming agents, such as psyllium hydrophilic mucilloid, may also be useful. Cholestyramine (Questran), which binds bile salts, and broad-spectrum antibiotics such as tetracycline may decrease diarrhea in diabetic patients with bacterial over-

growth. Because all of these agents treat symptoms rather than the underlying abnormality, therapeutic responses will vary.

Investigational Antidiarrheal Drugs

More recently, medications that alter small bowel mucosal secretion and absorption, such as clonidine, lidamidine, and octreotide acetate (Sandostatin), have been investigated. These drugs should be reserved for patients with moderate to severe watery diarrhea (stool collections > 500 g/d).

Studies have shown that stimulation of α_2 -adrenergic receptors normally promotes fluid and electrolyte absorption and inhibits anion secretion.^{21,25} Thus, research has turned to the α_2 -agonists to treat the more severe cases of diabetic diarrhea.

Clonidine, an α_2 -adrenergic agonist, presently approved as an antihypertensive medication, has significantly reduced the volume and frequency of stools in diabetic diarrhea.^{21,25,27,28} In animal studies, clonidine has also altered intestinal motility and slowed GI transit time.²⁷ Other studies have suggested that while clonidine enhances mucosal absorption and thereby lessens diarrhea, it may adversely affect gastroparesis. An average dosage of 1 to 1.5 mg/d (which is much higher than doses used for hypertension) is usually needed for diabetic diarrhea. The dosage should be increased gradually until symptoms improve. After a starting dosage of 0.1 mg orally every

12 hours, the clonidine dosage can be increased slowly by 0.1-mg increments over three days to about 0.6 mg every 12 hours.²⁵ Patients are able to tolerate these high doses because the severity of their autonomic neuropathy minimizes the central hypotensive effects. Clonidine is also available as a transdermal patch (Catapres-TTS).

Clonidine reduces stool frequency and volume in patients with diabetic diarrhea.

Potential side effects of clonidine include hypotension, sedation, and dry mouth. Slow withdrawal of clonidine is important to avoid rebound hypertension.²⁵

Lidamidine, an experimental nonnarcotic agent with partial α_2 -adrenergic properties similar to those of clonidine, has been shown to have antidiarrheal properties in diabetics. Goff²⁶ placed patients on lidamidine, 2 mg three times a day, and gradually increased the dosage as needed to a maximum of 20 mg/d. All patients had a 30% to 60% decrease in the frequency of bowel movements with improved stool consistency. No significant side effects were noted in this small study.

Somatostatin Analog. There are several case reports^{8,29,30} describing the use of a somatostatin analog, octreotide acetate, in the treatment of refractory diarrhea due to a variety of causes, including diabetes. Octreotide inhibits stimulated

DIABETIC GI COMPLICATIONS

water secretion in humans, increases gut absorptive capacity in vitro, and suppresses other potentially diarrheogenic GI hormones. One study²⁹ used a regimen of 50 µg to 150 µg SC twice daily.

Potential side effects of the somatostatin analog include malabsorption and worsening of diabetic control. Gallstone formation has been associated with octreotide use but whether it is drug related has not been determined.

DIABETIC CONSTIPATION

Constipation reportedly occurs in 20% to 60% of diabetics with neuropathy. It can lead to severe complications such as megacolon, impaction, stercoral ulcer, volvulus, and perforation.^{1-5,8,31} Chronic intestinal pseudo-obstruction may present late in the course of the disease.

Constipation has been reported in 20% to 60% of diabetics with neuropathy.

Once again, it is necessary to review the patient's medications to identify agents, such as antacids, narcotics, calcium channel blockers, and tricyclic antidepressants, that may inhibit colonic motility. Physical examination and abdominal x-ray should rule out ileus, bowel obstruction, and impaction. Colonoscopy or barium enema may be indicated to rule out occult malignancy, and manual disimpaction may be required

before a successful bowel regimen can be started.

Battle³¹ found that diabetic patients without constipation had blunted and delayed myoelectrical and colonic motor responses to a test meal, while constipated patients demonstrated no colonic myoelectric activity. Some patients with constipation have responded to metoclopramide and neostigmine methylsulfate, which suggests that although colonic muscle can be favorably affected, the abnormality can be traced to the nerve supply or neurohormonal control.

A multitude of agents—bulking agents, emollients, lubricants, hyperosmotic agents, and stimulants—has been used for the symptomatic treatment of constipation, with varying success. Some authors advocate a trial of a high-fiber diet or a bulking agent. These approaches may be useful in patients with mild symptoms, but they should not be used in those with marked activity limitations from peripheral neuropathy. Also, bulk agents may increase symptoms in patients with slow transit time.⁴

Bulking agents, emollients, lubricants, hyperosmotic agents, and stimulants have all had varying success in constipated diabetics.

Motility-Altering Drugs

Although laxatives containing senna should be avoided because of their neuropathic effects, most stimulant laxatives

can be used as diabetic constipation therapy.

Stimulant laxatives—available in both oral forms and suppositories—such as bisacodyl, phenolphthalein, cascara sagrada, and danthron, may be needed in some patients. Bisacodyl has been shown to stimulate the mucosal nerve plexus of the colon. Other stimulant laxatives, such as phenolphthalein, alter colonic absorption and secretion. Stimulant laxatives may cause severe cramping, electrolyte imbalances, metabolic acidosis and alkalosis, dermatologic reactions, and, in rare instances, hepatotoxicity.

Prokinetic Agents

Other agents thought to act at the neuromuscular level may ameliorate constipation in diabetes more effectively; however, controlled trials have not yet been done. Metoclopramide has been somewhat successful in relieving constipation in diabetics. Battle³¹ found dose-related increases in colonic motility in both normal patients and diabetics receiving metoclopramide.

Anecdotal reports^{12,15} suggest that cisapride may improve diabetic constipation, and Kreek successfully treated two patients with idiopathic constipation with naloxone, a specific opiate antagonist that accelerates bowel transit time.³²

IN CONCLUSION

Various agents are available that may relieve symptoms related to dia-

continued on page 77

DIABETIC GI COMPLICATIONS

continued from page 74

betic autonomic neuropathy of the GI tract. Where no single agent has been shown to be effective, a combination of medications may be necessary. The use of specific combinations needs to be explored further, but with careful monitoring, an effective medical regimen can be developed in most cases to relieve the symptoms of diabetic gastroparesis, diabetic diarrhea, and constipation. Regardless of which drugs are used to treat diabetic GI complications, maintaining tight blood glucose control is important.

References

1. Feldman M et al: Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 1983;98:378-384.
2. Goyal RK et al: Gastrointestinal manifestations of diabetes mellitus. *Med Clin North Am* 1971;55:1031-1044.
3. Keshavarzian A, Iber FL: Gastrointestinal involvement in insulin-requiring diabetes mellitus. *J Clin Gastroenterol* 1987;9:685-692.
4. Sack TL, Sleisenger MH: Diabetes mellitus and the gastrointestinal tract. In Sleisenger MH, Fordtran JS (eds): *Gastrointestinal Disease*. 4th ed. Philadelphia, W.B. Saunders Co., 1989, p. 494-500.
5. Taub S et al: Gastrointestinal manifestations of diabetes mellitus. *Diabetes Care* 1989;2:437-447.
6. Pellegrini CA et al: Diagnosis and treatment of gastric emptying disorders: Clinical usefulness of radionuclide measurements of gastric emptying. *Am J Surg* 1983;145:143-151.
7. Saltzman MB, McCallum RW: Diabetes and the stomach. *Yale J Biol Med* 1983;56:179-187.
8. Tsai S, Vinic AI: Diabetic diarrhea and somatostatin. *Ann Intern Med* 1986;104:894.
9. Barnett JL, Owyang C: Serum glucose concentration as a modulator of interdigestive gastric motility. *Gastroenterology* 1988;94:759-764.
10. Malagelada J et al: Gastric motor abnormalities in diabetic and postvagotomy gastroparesis: Effect of metoclopramide and bethanechol. *Gastroenterology* 1980;78:286-293.
11. Feldman M et al: Effect of cisapride on gastric emptying of indigestible solids in patients with gastroparesis diabeticorum: a comparison with metoclopramide and placebo. *Gastroenterology* 1987;92:171-174.
12. McCallum RW: Review of the current status of prokinetic agents in gastroenterology. *Am J Gastroenterol* 1985;80:1008-1016.
13. Schade RR et al: Effect of metoclopramide on gastric liquid emptying in patients with diabetic gastroparesis. *Dig Dis Sci* 1985;30:10-15.
14. Snape WJ et al: Metoclopramide to treat gastroparesis due to diabetes mellitus. *Ann Intern Med* 1982;96:444-446.
15. Horowitz M et al: Effect of cisapride on gastric and esophageal emptying in insulin-dependent diabetes mellitus. *Gastroenterology* 1987;92:1899-1907.
16. Trappnell BC et al: Metoclopramide suppositories in the treatment of diabetic gastroparesis. *Arch Intern Med* 1986;146:2278-2279.
17. Horowitz M et al: Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. *Dig Dis Sci* 1985;30:1-9.
18. *Physicians' Desk Reference*. Oradell, NJ: Medical Economics Company Inc., 1988.
19. Heer M et al: Diabetic gastroparesis: Treatment with domperidone—A double-blind, placebo-controlled trial. *Digestion* 1983;27:214-217.
20. Brady PG, Richardson R: Gastric bezoar formation secondary to gastroparesis diabeticorum. *Arch Intern Med* 1977;137:1729.
21. Chang EB et al: Experimental diabetic diarrhea in rats: Intestinal mucosal denervation hypersensitivity and treatment with clonidine. *Gastroenterology* 1986;92:564-569.
22. Goldstein F et al: Diabetic diarrhea and steatorrhea: Microbiologic and clinical observations. *Ann Intern Med* 1970;72:215-218.
23. Miller LJ: Small intestinal manifestations of diabetes mellitus. *Yale J Biol Med* 1983;56:189-193.
24. Yang R et al: Gastrointestinal tract complications of diabetes mellitus. *Arch Intern Med* 1984;144:1251-1256.
25. Fedorak RN et al: Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985;102:197-199.
26. Coff JS: Diabetic diarrhea and lidamidine. *Ann Intern Med* 1984;101:874.
27. Schiller LR et al: Studies of the anti-diarrheal action of clonidine: Effects of motility and intestinal absorption. *Gastroenterology* 1985;89:982-988.
28. Roof LW: Treatment of diabetic diarrhea with clonidine. *Am J Med* 1987;83:603-604.
29. Dudl RJ et al: Treatment of diabetic diarrhea and orthostatic hypotension with somatostatin analogue SMS 201-995. *Am J Med* 1987;83:584-588.
30. Maron PN et al: Effect of long-acting somatostatin analogue (SMS 201-995) in a patient with pancreatic cholera. *N Engl J Med* 1985;312:17-21.
31. Battle WM et al: Colonic dysfunction in diabetes mellitus. *Gastroenterology* 1980;79:1217-1221.
32. Kreek MJ et al: Naloxone, a specific opioid antagonist, reverses chronic idiopathic constipation. *Lancet* 1983;1:261.



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cerebrospinal fluid) separates the inner dura from the arachnoid.

dural ad. of relating to or affecting the dura.

dwarfism *n.* abnormally short stature from any cause. The most common type of dwarf is the *achondroplastic dwarf* (see *achondroplasia*). *Pituitary dwarfs* have a deficiency of growth hormone due to a defect in the pituitary gland; they are well proportioned and show no mental retardation, but (unlike *achondroplastic dwarfs*) have a genetic defect in their response to growth hormone. Dwarfism is also associated with thyroid deficiency (see *cretinism*), in which both physical and mental development is retarded; chronic diseases such as rickets, renal failure, and intestinal malabsorption.

dynamometer *n.* a device for recording the force of a muscular contraction. A small hand-held dynamometer may be used to record the strength of a patient's grip. A special optical dynamometer measures the action of the muscles controlling the shape of the lens of the eye.

dynes *n.* a unit of force, equal to the force required to impart to a mass of 1 gram an acceleration of 1 centimeter per second per second. 1 dyne = 10^{-5} newton.

dynia *n.* *suffix denoting* pain.

dynorphin *n.* (in the rectum).

dysphylis *n.* a drug that relaxes bronchial muscle and stimulates heart muscle. It is used to relieve symptoms in asthma and bronchitis and to treat congestive heart failure. It is administered by mouth, injection, or in suppositories and may cause nausea and vomiting, headache, palpitations, and dizziness, especially following injection. See *also* bronchodilator. Trade names: *Dibor*, *Nedophylis*.

dys- *prefix denoting* difficult, abnormal, or impaired. Examples: *dyslexia* (difficulty in reading); *dysentery* (impairment of waste); *dysarthria* (a speech disorder in which the pronunciation is unclear although the linguistic content and meaning are normal).

dysbarism *n.* any clinical syndrome due to a difference between the atmospheric pressure outside the body and the pressure of air or gas within a body cavity (such as the paranasal sinuses or the middle ear). See *compressed air illness*.

dyspareunia *n.* any disturbance of the will or of the mental processes that lead to purposeful action.

dyspareunia *n.* a form of constipation resulting from a long period of voluntary suppression of the urge to defecate. The rectum becomes distended with feces and bowel movements are difficult or painful.

dyspareunia *n.* a condition due to faulty ossification of cartilage, resulting in devel-

opment of many benign tumors (see *chondroma*). The involved tissue may become deformed.

dyspareunia *n.* an abnormal state of the part of the body, especially one in which the normal development or metabolism of the tissue is disturbed. The term is used in classical medicine to describe the imbalance of the four humors, which is believed to be the basic cause of disease.

dyspareunia *n.* (achondroplastic) a disease in which the normal development of the body is disturbed. It is often recognized by the patient to tap with his fingers on the back of his other hand. It is a disease of the cerebellum.

dyspareunia *n.* an infection of the intestines causing severe diarrhea with blood and mucus. *Acute dysentery* (common) is caused by the protozoan *Entamoeba histolytica* and results in ulcers of the intestines and occasionally in the formation of abscesses in the liver (see *abscess*), lungs, testes, or brain. The protozoa spread by food or water contaminated by infected feces. Symptoms appear even years after infection and include fever, indigestion, loss of weight, and pain. Prolonged treatment with sulfa drugs is effective in treating the disease.

Anemic dysentery is mainly caused by tropical and subtropical countries. *Bacillary dysentery* is caused by bacteria of the genus *Shigella* and is spread by water contaminated by their feces. Epidemics are common in overcrowded insanitary conditions. Symptoms develop 1-6 days after infection, including diarrhea, cramping, and fever. They persist for about a week. An infection causing serious dehydration and bleeding from the gut. In most cases, the fluid losses are replaced by giving 7-10 days' antibiotics or be given to eliminate the bacteria. *Cholera*.

dyspareunia *n.* the abnormal and unpleasant sensations felt by a patient with partial damage to a peripheral nerve whose skin is touched. Compare *paresthesia*.

dyspareunia *n.* failure of the ovaries or testes to develop (see *Turner's syndrome*).

dyspareunia (germinoma, gonocystoma) a malignant tumor of the ovary, thought to arise from primitive germ cells. It is homologous to the "seminoma" of the testis. About 15% of such tumors affect both ovaries; outside the ovary they have been reported in the anterior mediastinum and a

ical or physical factors may be responsible (see *vaginismus*).

dyspareunia (adfection) *n.* disordered digestion; usually applied to pain or discomfort in the lower chest or abdomen after eating and sometimes accompanied by nausea or vomiting. *-dyspareunia ad.*

dyspareunia *n.* a condition in which the action of swallowing is either difficult to perform, painful (see *odynophagia*), or in which swallowed material seems to be held up in its passage to the stomach. It is caused by painful conditions of the mouth and throat, obstruction of the pharynx or esophagus by disease of the wall or pressure from outside, or by abnormalities of muscular activity of the pharynx or esophagus.

dyspareunia *n.* see *aphasia*.

dyspareunia *n.* difficulty in speaking due to a disorder of the larynx, vocal cords, tongue, or mouth. Compare *dysarthria*, *aphasia*.

dyspareunia (aboplasia, heteroplasia) *n.* abnormal development of skin, bone, or other tissues. See *also* fibrous dysplasia.

dyspareunia *n.* labored or difficult breathing. The term is often used for a sign of labored breathing apparent to the doctor, *breathless*, *respiratory* being used for the subjective feeling of labored breathing. Dyspnea can be due to obstruction to the flow of air into and out of the lungs (as in bronchitis and asthma), various diseases affecting the tissue of the lungs (including pneumoconiosis, emphysema, tuberculosis, and cancer), and heart disease.

dyspareunia *n.* see *apud*.

dyspareunia ad. describing a "personality disorder" characterized by callous unconcern for others, irresponsibility, violence, disregard for social rules, and an incapacity to maintain enduring relationships.

dyspareunia (asynapsis) *n.* lack of coordination, especially clumsy uncoordinated movements found in patients with disease of the cerebellum. They include *dysmetria* (the application of inappropriate force for a movement), *intention tremor*, *dysdiadochokinesis*, and a staggering wide-based gait.

dystocia *n.* difficult birth, caused by abnormalities in the fetus or the mother. The most common causes of *fetal dystocia* are excessive size or malpresentation. *Maternal dystocia* may result if the pelvis is abnormally small, the womb muscles fail to contract, or the neck of the womb fails to expand. If the cause of dystocia cannot be eliminated, it may be necessary to deliver the baby by cesarean section or to operate in such a way that it can be removed with the minimum possible risk to the mother.

dystonia *n.* a postural disorder caused by disease of the "basal ganglia" in the brain.

dyspareunia *n.* a condition in which the action of swallowing is either difficult to perform, painful (see *odynophagia*), or in which swallowed material seems to be held up in its passage to the stomach. It is caused by painful conditions of the mouth and throat, obstruction of the pharynx or esophagus by disease of the wall or pressure from outside, or by abnormalities of muscular activity of the pharynx or esophagus.

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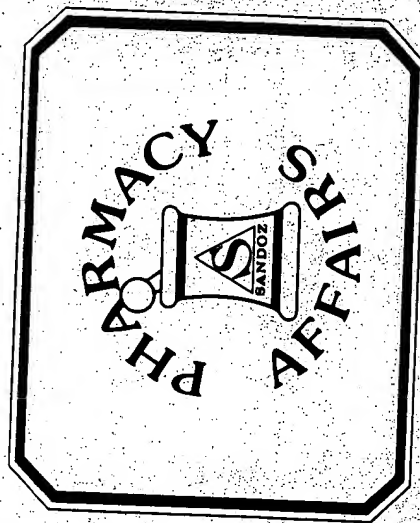
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community with park and
(*Lepidium sativum*) of the
pungent basal leaves
isomatous Old World vale-
for its fragrant tiny flowers
ian
under *Garden* †1791 Scot.
ardien) of Old World tropi-
with showy fragrant white or

MMONPLACE
tin to ONF wardrobe ward-
s 2: a private room: BED-

arde à l'aul look out for the
a warning cry when it was
vs into the streets
ound Table and nephew of

: GAR
a gigantic king in Rabelais'
and drink
ntua) (1596): of tremendous
sterfalls)
(-g-a-lin) [MF *gargouiller*,
l (a liquid) in the mouth or
s b: to cleanse or disinfect
ter with a gargling sound
as if gargling
gling 2: a sound of or like

r. MF
1 a
nan or
ter to
a gro-
ith an



gargoyle 1a

wom-
orn by
open
s, low
found
gion
own) (1545) 1: clothed in
LASHY b: offensively or dis-
ly showy syn see GAUDY —

arlande) (14c) 1: WREATH.

nd 2: to adorn with or as if

l'ac, fr. *gar* spear + *l'ac* leek
o'pan bulbous herb (*Allium*
ed for its pungent compound
y plant of the same genus 2

ing or prepared with garlic
id dried garlic and salt
nment, fr. OF, fr. *garnir* to
le of clothing
f with a garment
avelers that folds in half and

r. grenier, fr. L *granarium*, fr.
a: GRANARY b: a grain bin

ATION
rn-rin, 'gär-nä- (14c) 1 a
as if in a granary (volumes in
e labors — Reinhold Niebuhr)

CUMULATE, COLLECT
F, fr. *grenat*, adj., red like a
granate] (14c) 1: a brittle
icate mineral that has a vitre-
also in massive form and in
mica schist, and is used as a
a variable color averaging a

ff(-ä-ras) adj
paper with crushed garnet as

garnier †1904 Fr. geologist]
ous nickel magnesium silicate
el

miss, stem of *garnir* to warn,
OHG *warnōn* to take heed —
EMBELLISH b: to add decora-

2: to equip with accessories

IN
ORNAMENT 2: something (as
ish food or drink 3 a: an
a new inmate of an English
new worker

person who is served with a
to serve with a garnishment
authority

0) 1: GARNISH 2: a legal
achment of property to satisfy
from wages to satisfy a credi-

gar-ni-ture 'gär-ni-char, -nə-'chür n [MF. equipment, alter. of OF
garniture, fr. *garnir*] (1667) 1: EMBELLISHMENT, TRIMMING 2: a set
of decorative objects (as vases, urns, or clocks)

gar-pike 'gär-pik n (1776): GAR b
gar-ret 'gar-at n [ME *garrete* watchtower, fr. MF *garite* watchtower,
refuge, fr. OF *garir*] (14c): a room or unfinished part of a house just
under the roof

'gar-rison 'gar-sən n [ME *garisoun* protection, fr. OF *garison*, fr.
garir to protect, of Gmc origin; akin to OHG *werien* to defend — more
at WEIR] (15c) 1: a military post; esp: a permanent military installa-
tion 2: the troops stationed at a garrison

'garrison vt 'gar-ri-soned, 'gar-ri-son-ing 'gar-s(ə)-nɪŋ (1569) 1
to station troops in 2 a: to assign as a garrison b: to occupy
with troops

'garrison cap n (1944): a visorless folding cap worn as part of a mili-
tary uniform — compare SERVICE CAP

Gar-rison finish 'gar-sən-ə n [prob. fr. Edward "Snapper" Garri-
son, 19th cent. Am. jockey] (1935): a finish in which the winner comes
from behind at the end

'garrison house n (1676) 1: a house fortified against Indian attack 2
BLOCKHOUSE 3: a house having the second story overhanging the
first in the front

'garrison state n (1937): a state organized to serve primarily its own
need for military security; also: a state maintained by military power

gar-ron 'gar-an, gə-'ron n [Ir *gearrán* & ScGael *gearran*, *gelling*] (1540) Scot & Irish: a small sturdy workhorse

'gar-roter or 'gar-rotte 'gə-'rät, -röt; 'gar-at n [Sp *garrote*] (1622) 1 a
a method of execution by strangulation b: the apparatus used 2
an implement (as a wire with a handle at each end) for strangulation

'garrote or 'garrotte vt 'gar-rot-ed or 'gar-rot-ed; 'gar-rot-ing or 'gar-
rotting (1851): to strangle with or as if with a garrote — *gar-rot-er*
n

gar-ru-li-ty 'gə-'rü-lä-tē, gə-' n (1581): the quality or state of being
garrulous

gar-ru-lous 'gar-rə-ləs also 'gar-yə- adj [L *garrulus*, fr. *garrare* to chat-
ter — more at CARE] (ca. 1611) 1: given to prosy, rambling, or te-
dious loquacity: pointlessly or annoyingly talkative 2: WORDY 1 (~
speeches) syn see TALKATIVE — *gar-ru-lous-ly* adv — *gar-ru-lous-
ness* n

'gar-ter 'gär-tər n [ME, fr. ONF *gartier*, fr. *garet* bend of the knee, of
Celt origin; akin to W *gar* shank] (14c) 1 a: a band worn to hold up
a stocking or sock b: a band worn to hold up a shirt sleeve c: a
strap hanging from a girdle or corset to support a stocking 2 cap a
the British Order of the Garter; also: the blue velvet garter that is its
badge b: membership in the order

'garter vt (15c): to support with or as if with a garter
garter snake n (1769): any of a genus (*Thamnophis*) of harmless viv-
iparous American snakes with longitudinal stripes on the back

garth 'gärth n [ME, fr. ON *garthr* yard; akin to OHG *gart* enclosure
— more at YARD] (14c): a small yard or enclosure: CLOSE

gar-vey 'gär-ve n, pl *garveys* [prob. fr. the name *Garvey*] (ca. 1896)
a small scow esp. of the New Jersey coast

'gas 'gas n, pl *gases* also *gas-es* [NL, alter. of L *chaos* shape, chaos]
(1779) 1: a fluid (as air) that has neither independent shape nor vol-
ume but tends to expand indefinitely 2 a: a combustible gas or
gaseous mixture for fuel or lighting; esp: NATURAL GAS b: a gaseous
mixture used to produce anesthesia d: a substance that can be used
to produce a poisonous, asphyxiating, or irritant atmosphere 3
empty talk: POMBAST 4: GASOLINE; also: the accelerator pedal of an
automotive vehicle 5: driving force: ENERGY (I was young, and full
of ~ — H. L. Mencken) (ran out of ~ in the seventh inning) 6 slang
something that gives pleasure: DELIGHT (the party was a ~)

'gas vb *gas* *gas* *gas* *gas* (1852) 1: to talk idly or garrulously 2
to give off gas 3: to fill the tank (as of an automobile) with gasoline
— usu. used with up ~ vt 1: to supply with gas or esp. gasoline (~
up the car) 2 a: to treat chemically with gas b: to poison or other-
wise affect adversely with gas 3 slang: to please greatly

gas-bag 'gas-bäg n (1827) 1: a bag for holding gas 2: an idle or
garrulous talker

gas chamber n (1945): a chamber in which prisoners are executed by
poison gas

gas chromatograph n (1958): an instrument used to separate a sam-
ple into components in gas chromatography

gas chromatography n (1952): chromatography in which the sample
mixture is vaporized and injected into a stream of carrier gas (as nitro-
gen or helium) moving through a column containing a stationary phase
composed of a liquid or particulate solid and is separated into its com-
ponent compounds according to their affinity for the stationary phase —
gas chromatographic adj

gas-con 'gas-kən n (14c) 1 cap a: a native of Gascony b: the
Romance speech of Gascony 2: a boastful swaggering person —
Gascon adj

gas-co-nade 'gas-kə-'näd n [F *gasconade*, fr. *gasconner* to boast, fr.
gascon gascon, boaster] (1709): BRAVADO, BOASTING — *gasconade* vi
— *gas-con-ade* n

gas-eous 'ga-sē-əs, 'ga-shəs adj (1799) 1: having the form of or
being gas; also: of or relating to gases 2 a: lacking substance or
solidity b: GASSY 3 (trick phrases and ~ circumlocutions — Edwin
Newman) — *gas-eous-ness* n

gas fitter n (ca. 1858): a worker who installs or repairs gas pipes and
appliances

gas gangrene n (1914): progressive gangrene marked by impregna-
tion of the dead and dying tissue with gas and caused by one or more
toxin-producing clostridia

gas-guz-zler 'gas-'guz-lər, -'gə-zə- n (1973): a usu. large automobile
that gets relatively poor mileage — *gas-guz-zling* (-lɪŋ) adj

'gash 'gəsh n (1548) 1: a deep long cut in flesh 2: a deep narrow
depression or cut (cut a ~ through the forest) (a ~ in the hull)
'gash vb [alter. of ME *garsen*, fr. ONF *garser*, fr. (assumed) VL *chariss-*
are, fr. Gk *charassin* to scratch, engrave] vt (1570): to make a gash in
~ vi: to make a gash: CUT

'gash adj [origin unknown] (1706) 1 chiefly Scot: KNOWING, WITTY 2
chiefly Scot: well-dressed: TRIM

gas-holder 'gas-höl-dər n (1802): a container for gas; esp: a huge
cylindrical tank for storing fuel gas under pressure

gas-house 'gas-haus n (1880): GASWORKS

gas-i-fi-ca-tion 'ga-sə-'fä-'kə-shən n (1812): conversion into gas; esp:
conversion of coal into natural gas

gas-i-ty 'ga-sə-'tɪ vb -i-fied; -i-ty-ing vt (ca. 1828): to convert into
gas (~ coal) ~ vi: to become gaseous — *gas-i-fi-er* 'ga-sə-'fä-(ə)r n

gas-ket 'gas-kət n [perh. modif. of F *garçette*] (ca. 1889): a material
(as rubber) or a member (as an O-ring) used to make a joint fluid-tight

gas-kin 'gas-kən n [prob. short for *galligaskins*] (1573) 1 pl, obs
HOSE, BREECHES 2: a part of the hind leg of a quadruped between the
stifle and the hock — see HORSE illustration

gas-light 'gas-'lit, -'lɪt n (1808) 1: light made by burning illuminat-
ing gas 2: a gas flame or gas lighting fixture

gas-liquid chromatography n (1952): gas chromatography in which
the stationary phase is a liquid — *gas-liquid chromatographic* adj

gas-lit 'gas-'lit, -'lɪt adj (1837): illuminated by gaslight

gas log n (1885): a hollow perforated imitation log used as a gas
burner in a fireplace

gas mask n (1915): a mask connected to a chemical air filter and used
to protect the face and lungs from toxic gases; broadly: RESPIRATOR 1

gas-o-gene 'ga-sə-'jən n [F *gazogène*, fr. *gaz* gas (fr. NL *gas*) + -o- +
-gène -gen] (ca. 1853) 1: a portable apparatus for carbonating liquids
2: an apparatus carried by a vehicle to produce gas for fuel by partial
burning of charcoal or wood

gas-o-hol 'ga-sə-'höl n [blend of *gasoline* and *alcohol*] (1977): a fuel
consisting of a blend usu. of 10 percent ethyl alcohol and 90 percent
gasoline

gas oil n (1901): a hydrocarbon oil used as a fuel oil; esp: a petroleum
distillate intermediate in boiling range and viscosity between kerosene
and lubricating oil

gas-olier 'ga-sə-'liər n [alter. of *gaselier*, fr. *gas* + -elier (as in *chande-
lier*)] (1905): a gaslight chandelier

gas-o-line also gas-o-lene 'ga-sə-'lən, 'ga-sə-' also -zə- n [gas + -ol
+ -line or -ene] (1865): a volatile flammable liquid hydrocarbon mix-
ture used as a fuel esp. for internal combustion engines and usu.
blended from several products of natural gas and petroleum — *gas-o-
lin-ic* 'ga-sə-'lē-nik, -'lɪ- adj

gas-om-e-ter 'ga-'sə-mə-'tər n [F *gazomètre*, fr. *gaz* + -o- + -mètre
-meter] (1808) 1: GASHOLDER 2: a laboratory apparatus for holding
and measuring gases

gas-operated adj (1944) of a firearm: using part of the force of ex-
panding propellant gases to operate the action

gasp 'gəsp vb [ME, akin to ON *geispa* to yawn] vi (14c) 1: to catch
the breath convulsively and audibly (as with shock) 2: to breathe
laboriously ~ vi: to utter in a gasping manner — *gasp* n

gasp-er 'gəsp-ər n (1914) slang Brit: CIGARETTE

gas plant n (ca. 1909): FRAXINELLA

gas ring n (1901): a ring-shaped portable gas burner for cooking

gassed 'gəst adj (ca. 1925): DRUNK 1

gas-ser 'gas-sər n (ca. 1944) slang: something outstanding

gas station n (1925): SERVICE STATION 1

gas-sy 'ga-sē adj *gas-si-er*, -est (1575) 1: full of or containing gas
2: having the characteristics of gas 3: characterized by many words
but little content: empty verbose — *gas-si-ly* 'ga-sə-'lɪ- adv — *gas-
si-ness* n

gast 'gəst vt [ME, fr. *gast*, *ghost* — more at GHOST] (14c) obs
SCARE (~ed by the noise I made, full suddenly he fled — Shak.)

Gast-ar-bei-ter 'gəst-'jä-r-'bi-tər n, pl *Gastarbeiter* also *Gastar-
beiters* [G, fr. *Gast* guest + *Arbeiter* worker] (1970): a foreign worker
esp. in Germany

gas-ter 'gas-tər n [Gk *gastēr*] (ca. 1909): the enlarged part of the
abdomen behind the pedicle in hymenopterous insects (as ants)

gas-tight 'gas-'tɪt adj (1831): impervious to gas — *gas-tight-ness* n

gas-ness 'gas(t)-nəs n (14c) obs: FRIGHT, TERROR

gastr- or gastro- also gastr- comb form [Gk, fr. *gastēr*, *gastēr*] 1
stomach (*gastrorectomy*) 2: gastric and (*gastrointestinal*)

gas-trea also gas-traea 'ga-'strē-ə n [NL, fr. Gk *gastēr*, *gastēr*] (1879)
a hypothetical metazoan ancestral form corresponding in organiza-
tion to a simple invaginated gastrula

gas-trec-to-my 'ga-'strēk-tə-'mē n, pl -mies [ISV] (1886): surgical
removal of all or part of the stomach

gas-tric 'gas-'trɪk adj [Gk *gastēr*, *gastēr*, alter. of (assumed) Gk *grastēr*,
fr. Gk *grān* to gnaw, eat] (1656): of or relating to the stomach

gastric gland n (1900): any of various glands in the walls of the stom-
ach that secrete gastric juice

gastric juice n (ca. 1736): a thin watery acid digestive fluid secreted
by glands in the mucous membrane of the stomach

gastric ulcer n (ca. 1910): a peptic ulcer situated in the stomach

gas-trin 'gas-'trɪn n (1905): any of various polypeptide hormones
that are secreted by the gastric mucosa and induce secretion of gastric
juice

gas-tri-tis 'ga-'stri-təs n (1806): inflammation esp. of the mucous
membrane of the stomach

gas-troc-ne-mi-us 'gas-(t)rək-'nē-mē-əs, -trək- n, pl -mii 'mē-'nɪ
[NL, fr. Gk *gastroknēmē* calf of the leg, fr. *gastēr* + *knēmē* shank —
more at HAM] (1676): the largest and most superficial muscle of the
calf of the leg arising by two heads from the condyles of the femur and
attaching to a tendon that becomes part of the Achilles tendon

gas-tro-du-o-de-nal 'gas-tro-'dɪ(y)ü-'dē-nəl, -d(y)ü-'dē-nəl adj
(1854): of, relating to, or involving the stomach and the duodenum

gas-tro-en-ter-i-tis 'gas-tro-'en-tə-'rɪ-təs n (ca. 1829): inflammation
of the lining membrane of the stomach and the intestines

gas-tro-en-ter-ol-o-gy 'gas-tro-'en-tə-'rɪ-ə-lə-jɪ n [ISV] (ca. 1904): a branch
of medicine concerned with the structure, functions, diseases, and pa-
thology of the stomach and intestines — *gas-tro-en-ter-ol-o-gi-cal*
'rə-'lä-jɪ-kəl adj — *gas-tro-en-ter-ol-o-gist* 'en-tə-'rɪ-ə-lə-jɪst n

\ə\ about \ʌ\ kitten, F table \ər\ further \ə\ ash \ä\ ace \ä\ mop, mar
\ä\ out \ə\ chin \e\ bet \e\ easy \ə\ go \i\ hit \i\ ice \i\ job

\j\ sing \d\ go \ə\ law \ə\ boy \i\ thin \i\ the \i\ loot \u\ foot
\y\ yet \ə\ vision \ä\ k, ʔ, æ, œ, u, ɛ, ɪ, see Guide to Pronunciation